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09/460,216	12/13/1999	GRAHAM P. ALLAWAY	50875-F-PCT-	2202
23432 7590 06/23/2009 COOPER & DUNHAM, LLP 30 Rockefeller Plaza 20th Floor NEW YORK, NY 10112			EXAMINER PARKIN, JEFFREY S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Application No.: 09/460,216

Applicants: Allaway, G. P., et al.

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Detailed Office Action

37 C.F.R. § 1.114

A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection on 24 March, 2009. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114. Applicants' response did not include any claim amendments. Claims 61 and 66 are pending in the instant application.

37 C.F.R. § 1.98

The information disclosure statement filed 02, April, 2009, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 61 and 66 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

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time the application was filed, had possession of the claimed invention. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398, (Fed. Cir. 1997). *Fiers v. Revel Co.*, 984 F.2d 1164, 25 U.S.P.Q.2d 1601, (Fed. Cir. 1993). *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 U.S.P.Q.2d 1016, (Fed. Cir. 1991). *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609, (Fed. Cir. 2002). *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90 (C.C.P.A. 1976). *University of Rochester v. G. D. Searle & Co., Inc.*, 358 F.3d 916, 69 U.S.P.Q.2d 1886 (C.A.F.C. 2004). The claims are directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a CD4⁺ cell by contacting said cell with a **CCR5 chemokine receptor antagonist** that binds to CCR5, blocks fusion by macrophage-tropic isolates, permits fusion by T-cell-tropic isolates, and does not activate an inflammatory response. Claim 66 further specifies that the CCR5 chemokine receptor antagonist may be a polypeptide.

As previously set forth, to satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had **possession** of the claimed invention. See, e.g., *Vas-Cath, Inc., v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116. The issue raised in this application is whether the original application provides adequate support for the broadly claimed genus of **antagonists** that are capable of abrogating HIV-1 infection by binding to the CCR5 chemokine receptor. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words,

structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 U.S.P.Q.2d 1961, 1966 (Fed. Cir. 1997). The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the biomolecule of interest. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993). *In re Deuel*, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995). A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1571, 39 U.S.P.Q.2d 1895, 1905 (Fed. Cir. 1995). The court noted in this decision that a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not reasonably lead those skilled in the art to any particular species.

An applicant may show possession of an invention by disclosure of drawings or structural chemical formulas that are sufficiently detailed to show that applicant was in possession of the claimed invention as a whole. An applicant may also show that an invention is complete by disclosure of sufficiently

detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. For some biomolecules, examples of identifying characteristics include a nucleotide or amino acid sequence, chemical structure, binding affinity, binding specificity, and molecular weight. The written description requirement may be satisfied through disclosure of function and minimal structure when there is a well-established correlation between structure and function. Without such a correlation, the capability to recognize or understand the structure from the mere recitation of function and minimal structure is highly unlikely. In the latter case, disclosure of function alone is little more than a wish for possession; it does not satisfy the written description requirement. *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1566, 43 U.S.P.Q.2d 1398, 1404, 1406 (Fed. Cir. 1997), *cert. denied*, 523 U.S. 1089 (1998). *In re Wilder*, 736 F.2d 1516, 1521, 222 U.S.P.Q. 369, 372-3 (Fed. Cir. 1984). Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention.

The claims of the instant application are still broadly directed toward **any CCR5 chemokine receptor antagonist** that is capable of abrogating HIV-1 infection through CCR5 binding

interactions. The claims do not limit the genus to any particular type of compound (e.g., peptidyl, organic, fatty acid, etc.) or any particular subgenus of compounds (e.g., small molecular weight peptidyl inhibitors, antibody-based reagents, peptidomimetics, etc.). The disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. This method by itself does not lead the skilled artisan to any particular class of compounds. The disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. Thus the genus corresponding to the agent employed in the claimed assay encompasses an inordinate number of unrelated species (e.g., proteins, oligopeptides, retroinverso oligopeptides, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, small molecule inhibitors, etc.). It is noted that some data was supplied pertaining to a limited number of agents from two subgenuses. Specifically, a small number of β -chemokines were identified with inhibitory activity (e.g., the β -chemokines MIP-1 α and -1 β). These two chemokines are natural ligands for the CCR5 receptor. It was suggested that two chemokine antagonists, Met-RANTES and MCP-1(Δ 1-8), might be useful in the claimed methodology.

Although the specification does provide a small number of inhibitory agents, nevertheless, this limited number of species are insufficient to place the inventors in possession of the full genus of agents at the time of filing. First, the disclosure fails to provide any significant structural information concerning the molecular determinants (i.e., epitopes, structural domains, etc.) on CCR5 that modulate CCR5-

CD4-gp120 binding events. Thus, the skilled artisan would not be able to perform any type of rational drug-screening approach. Instead, putative antiviral agents would need to be identified through trial-and-error. Second, the disclosure fails to provide adequate guidance pertaining to the structures of any particular subgenus of inhibitory agents. The disclosure fails to provide any useful structural criteria for small molecule inhibitors, peptidomimetics, retroinverso polypeptides, antigen-antibody binding sites, etc. Thus, the skilled artisan cannot readily envisage the structure of any particular putative antiviral agent. Third, although the specification provides a generic screening assay to identify potential candidate molecules, nevertheless, this assay fails to lead the skilled artisan to any particular subgenus of inhibitory agent. Applicants are essentially relying upon others to identify putative antiviral agents that would meet the claim limitations. Fourth, the state-of-the-art as it pertains to HIV antiviral development is characterized by unpredictability. The CCR5 chemokine receptor is a large transmembrane spanning protein. It interacts with both gp120 and CD4 during virion-cell fusion events. These interactions may employ linear domains or conformational domains. However, the precise determinants modulating these binding interactions remain to be elucidated. Accordingly, it would be difficult for the skilled artisan to identify candidate agents because of the dearth of structural information. For instance, if the skilled artisan was employing a peptidomimetic, what is the appropriate amino acid sequence of said mimetic? If the skilled artisan is going to employ a small molecule organic inhibitor, what is the structure of this compound? The disclosure fails to address these concerns. Accordingly, the

skilled artisan would reasonably conclude that applicants were not in possession of the claimed genus of compounds at the time of filing.

Response to Arguments

As previously set forth, Applicants maintained that sufficient structural information was provided as evidenced by the ability of natural chemokine ligands to bind to, and inhibit, viral infectivity. Applicants were reminded that the claims are not limited to natural ligands of CCR5, but rather encompass any type of compound with antagonistic activity. The disclosure fails to provide any detailed structural information regarding those CCR5 chemokine receptor domains or regions that should be targeted for antiviral development. Which amino acids of CCR5 are involved in modulating viral infectivity? In the absence of such information, the skilled artisan can only guess as to which compounds might have the desired activities.

Applicants additionally maintained that multiple examples were provided concerning the identification of putative antivirals that meet the claimed limitations. Reference was made to a series of Mabs and the natural ligands for CCR5. The functional characteristics of the referenced antibodies are quite variable in terms of binding specificity and inhibitory activity. Nothing in the disclosure leads the skilled artisan to any particular region of CCR5. Moreover, the natural ligands of CCR5 are insufficient to enable the full breadth of the claimed invention which is directed toward a large genus of poorly defined compounds.

Applicants additionally argued that a specific screening assay was provided to identify compounds that meet the claimed

limitations. The examiner did not dispute that the FRET assay disclosed in the specification allows the skilled artisan to test any given compound for antiviral activity. However, this assay does not provide any detailed structural information about the compounds of interest or the molecular determinants modulating CCR5/CD4/gp120 binding interactions. Absent further detailed structural information, the skilled artisan cannot rationally design suitable antagonists.

Finally, applicants added that the level of skill in the art was relatively high thereby precluding the need for more detailed information. The examiner did not dispute this general assertion. However, it still does not lead the skilled artisan to any particular class of compounds or individual compounds other than the small representative examples provided. Accordingly, the rejection is proper and hereby maintained.

Scope of Enablement

Claims 61 and 66 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are directed toward a method of inhibiting HIV-1 macrophage-tropic infection of a CD4⁺ cell by contacting said cell with a **CCR5 chemokine receptor antagonist** that binds to CCR5, blocks fusion by macrophage-tropic isolates, permits fusion by T-cell-tropic isolates, and does not activate an inflammatory response. Claim 66 further specifies that the CCR5 chemokine receptor antagonist may be a polypeptide. A small number of β -chemokines were identified with inhibitory activity (e.g., the β -chemokines

MIP-1 α and -1 β). These two chemokines are natural ligands for the CCR5 receptor. It was suggested that two chemokine antagonists, Met-RANTES and MCP-1(Δ 1-8), might be useful in the claimed methodology.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claim breadth potentially encompasses a large genus of poorly defined compounds. The claim of the instant application is broadly directed toward **any antagonist** that is capable of abrogating HIV-1 infection through CCR5 binding interactions. The claims do not limit the genus to any particular type of compound (i.e., peptidyl, organic, fatty acid, etc.) or any particular family of compounds (small molecular weight peptidyl inhibitors, antibody-based reagents, etc.). The disclosure provides a generic *in vitro* resonance energy transfer (RET) screening assay that enables the skilled artisan to detect HIV-1 fusion events. This method by itself does not lead the skilled

artisan to any particular class of compounds. The disclosure also fails to provide sufficient structural/functional guidance pertaining to suitable compounds that can reasonably be expected to function in the claimed methodology. Thus the genus corresponding to the agent employed in the claimed assay encompasses an inordinate number of unrelated species (e.g., proteins, oligopeptides, retroinverso oligopeptides, polyclonal antibodies, monoclonal antibodies, chimeric antibodies, small molecule inhibitors, etc.).

2) The disclosure fails to provide a sufficient number of working embodiments. The only representative examples appear to be directed toward two chemokine antagonists, Met-RANTES and MCP-1(Δ 1-8). No other working embodiments are disclosed.

3) The disclosure fails to provide sufficient structural guidance pertaining to the molecular determinants modulating chemokine antagonist binding to CCR5. Although the β -chemokines are only ~8-10 kDa, their receptors are much larger complex proteins with multiple-membrane spanning domains. In order to practice the claimed invention, the skilled artisan would require a reasonable knowledge of those determinants modulating antagonist-receptor binding interactions. However, the specification is silent concerning this topic.

4) The disclosure fails to provide sufficient structural guidance pertaining to those classes of compounds that are capable of inhibiting HIV-1 macrophage-tropic binding interactions. The claims simply rely upon a limited number of functional limitations without providing sufficient structural guidance. As set forth *supra*, the claims could potentially encompass any class of CCR5 chemokine antagonist (i.e., β -chemokine analogues, peptidomimetics, antibodies, small molecule

inhibitors, etc.)). However, the disclosure fails to provide sufficient guidance pertaining to those classes of compounds that can reasonably be expected to function in the recited assay.

5) Moreover, it has been well-established that the development of suitable HIV-1 therapeutics has been a long and arduous process, often ending in failure (Öberg and Vrang, 1990; Yarchoan and Broder, 1992; Gait and Karn, 1995; Flexner and Hendrix, 1997). This is due to a number of considerations such as a failure to understand the molecular determinants modulating many viral protein and host cell factor interactions, the failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy, the failure of many compounds to have acceptable pharmacological profiles, despite initial favorable *in vitro* and *in vivo* activities, and the failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these molecular interactions. The disclosure fails to provide sufficient guidance pertaining to the aforementioned caveats. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Response to Arguments

Applicants maintained that sufficient structural guidance and a representative number of working embodiments was provided. These arguments were not persuasive for the reasons of record set forth *supra*. The disclosure fails to provide any detailed guidance pertaining to the molecular determinants modulating

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CCR5/CD4/gp120 binding interactions. Accordingly, nothing in the disclosure leads the skilled artisan to any other CCR5 antagonistic compounds other than the natural ligands provided and the group of Mabs with varying functional properties.

***Action Is Final, First Action Following Request for Continued
Examination under 37 C.F.R. § 1.114***

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 C.F.R. § 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 C.F.R. § 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 C.F.R. § 1.114. See M.P.E.P. § 706.07(b). Applicants are reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

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Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Larry R. Helms, can be reached at (571) 272-0832. Direct general status inquiries to the Technology Center 1600 receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

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Respectfully,

/Jeffrey S. Parkin/
Primary Examiner, Art Unit 1648

20 June, 2009